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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission

Application Number	09/735,743
Filing Date	December 12, 2000
First Named Inventor	Wei-mi Liu
Art Unit	1631
Examiner Name	Marianne Allen
Attorney Docket Number	3298.1

ENCLOSURES *(check all that apply)*

- ☒ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment / Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☒ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) ____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☒ Appeal Communication to TC **(Appeal Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) *(please identify below)*:

-Return Postcard.

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm	Affymetrix, Inc.		
Signature			
Printed Name	Wei Zhou		
Date	6/24/05	Reg. No.	44,419

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as EXPRESS MAIL Post Office to Addressee in an envelope addressed to: Mail Stop APPEAL BRIEF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below. ***EXPRESS MAIL LABEL: EV 500852259 US.***

Signature	Pamela Leong		
Typed or printed name	Pamela Leong	Date	6/24/05

PTO/SB/17 (12-04v2)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL for FY 2005

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT	($) 500.00

Complete if Known	
Application Number	09/735,743
Filing Date	December 12, 2000
First Named Inventor	Wei-min Liu
Examiner Name	Marianne Allen
Art Unit	1631
Attorney Docket No.	3298.1

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify) : _____

☒ Deposit Account Deposit Account Number: 01-0431 Deposit Account Name: Affymetrix, Inc.

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☒ Charge any additional fee(s) or underpayments of fee(s) Under 37 CFR 1.16 and 1.17 ☒ Credit any overpayments

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee($)	Fee($)	Fee($)	Fee($)	Fee($)	Fees Paid ($)
Utility	300	150	500	250	200	100	____
Design	200	100	100	50	130	65	____
Plant	200	100	300	150	160	80	____
Reissue	300	150	500	250	600	300	____
Provisional	200	100	0	0	0	0	____

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 30 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims		Extra Claims		Fee($)		Fee Paid ($)
____	-20 or HP=	____	x	____	=	____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		Extra Claims		Fee($)		Fee Paid ($)
____	- 3 or HP=	____	x	____	=	____

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims	
Fee ($)	Fee Paid ($)
____	____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

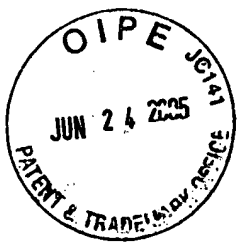
Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof		Fee ($)	Fee Paid ($)
____	- 100 =	____	/ 50 =	____	(round **up** to a whole number) x		= ____

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	500.0
Other (e.g., late filing surcharge) : Appeal brief fees under 37 CFR § 41.20(b)(2)	

SUBMITTED BY

Signature		Registration No. (Attorney/Agent) 44,419	Telephone 408-731-5000
Name (Print/Type)	Wei Zhou		Date December 12, 2000



PATENT
Attorney Docket No. 3298.1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicants: Wei-min Liu, et al

Serial No: 09/735,743

Filing Date: Dec. 12, 2000

Title: **Systems and Computer Software Products for Gene Expression Analysis**

Examiner: Marianne P. Allen

Group Art Unit: 1631

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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APPEAL BRIEF

I. Introduction

This is an appeal from the final rejection of the examiner dated May 26, 2004. This brief is accompanied by the requisite fees set forth in 37 C.F.R. § 41.20(b)(2).

II. Real Party in Interest

The real party in interest in this application is Affymetrix, Inc.

III. Related Appeals and Interferences

There are no related appeals or interferences material to this application.

IV. Status of the Claims

The application was filed as original application on December 12, 2000. The application, as originally filed contained 102 claims, of which 6 were independent (claims 1, 26, 39, 64, 77 and 102).

In an Office Action dated November 4, 2002, the examiner rejected claims 1-102.

On May 5, 2003, applicants cancelled claims 10, 22, 35, 48, 60, 73, 86 and 98; amended claims 11, 23, 24, 29, 39, 37, 43, 49, 52, 61, 62, 67, 74, 75, 77, 87, 90, 99, 100 and 102; and added claim 103.

In a Final Office Action dated July 24, 2003, the examiner rejected claims 1-9, 11-21, 23-34, 36-47, 49-59, 61-72, 74-85, 87-97 and 99-103.

On January 26, 2004, applicants filed an amendment after final rejection wherein the applicants amended claims 14, 39, 64 and 90.

On February 18, 2004, the examiner issued an Advisory Action maintaining the new matter rejection of claim 103; the enablement portion of the rejection and the art rejection.

On March 18, 2004, applicants filed a Request for Continued Examination.

On May 26, 2004, the examiner issued a Final Office Action rejecting claims 1-9, 11-21, 23-34, 36-47, 49-59, 61-72, 74-85, 87-97, 99-103.

On November 16, 2004 examiner and applicants' representative, Wei Zhou, participated on a telephonic interview. No agreement was reached.

On November 24, 2004, applicants filed an amendment after final rejection wherein the applicants amended claims 14, 39, and 103. A Notice of Appeal was filed with this amendment.

On December 17, 2004, the examiner issued an Advisory Action indicating that the proposed amendment after the final rejection overcame the new matter rejection under 35 U.S.C. § 112, 1st paragraph, with respect to claim 103. The Advisory Action indicated that all other rejections are maintained.

Accordingly, the status of the claims is as follows: Claims 1-2, 6-9, 11-12, 14-15, 26-27, 31-34, 36-40, 44-47, 49-53, 56-69, 61-65, 69-72, 74-78, 82-85, 87-91, and 93-103 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Claims 39-47, 49-51, 52-59, 64-72, and 74-76 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. Claims 1, 39, and 77 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Lockhart et al. (1996) in view of either Hogg et al. or Hollander et al.

The claims which are appealed herein are claims 1-9, 11-21, 23-34, 36-47, 49-59, 61-72, 74-85, 87-97, and 99-103.

V. Status of Amendments

Applicants amendment filed November 24, 2004 are deemed to be entered. The claims set forth in the Appendix include the amendments set forth in all amendments, including applicants' amendment after final rejection.

VI. Summary of the Claimed Subject Matter

The current invention provides methods, systems and computer software products suitable for analyzing data from gene expression monitoring experiments that employ multiple probes against a single target.

In one aspect of the invention, non-parametric statistical analysis is employed to analyze results of multiple probe gene expression experiments with control probes such as mismatch probes.

According to one aspect of the invention, the intensity values for the perfect match and mismatch probes (typically at least two) are used to analyze the presence, absence and level of the target. The multiple intensity values are used for a Wilcoxon rank test for detecting whether the perfect match probe intensities are significantly different from those of corresponding mismatch probes. For the Wilcoxon's test, a test statistic is selected and a *p*-value is typically generated using the test statistic. A call can be made

based upon the *p*-value and a threshold value. As it is well known to scientists, the selection of the threshold value is dependent upon the desired stringency of the test. The corresponding European Patent 1136933 covering the claimed invention in this application was granted on June 9, 2004.

The claims are directed to computer implemented methods are used for determining whether a RNA transcript (a product of gene expression) is present in a biological sample. The methods include step of providing a plurality of perfect match intensity values (PM_i) and mismatch intensity values (MM_i) for the transcript, where each of the PM_i is paired with one of the MM_I; calculating a *p*-value using one sided Wilcoxon's signed rank test, where the *p*-value is for a null hypothesis that θ=a threshold value and an alternative hypothesis that said θ> the threshold value, wherein said θ is a test statistic for intensity difference between the perfect match intensity values and mismatch intensity values; and indicating whether the transcript is present based upon the *p*-value.

In some embodiments, the testing statistic is $median(PM_i\text{-}MM_i)$. The threshold value may be zero. In some preferred embodiments, the threshold value is calculated using $\tau_1 = c_1\sqrt{median(PM_i)}$ wherein said c_I is a constant. Alternatively, the threshold value is calculated using: $\tau_1 = c_1\sqrt{mean(PM_i)}$ wherein c_I is a constant.

The presence, marginal present or absence (detected, marginally detected or undetected) of a transcript may be called based upon the *p* –value and significance levels.

Significance levels, α_1 and α_2 may be set such that: $0<\alpha_1<\alpha_2<0.5$. Note that for the one-sided test, if null hypothesis is true, the most likely observed *p*-value is 0.5, which is equivalent to 1 for the two-sided test. Let *p* be the *p*-value of one sided signed rank test. In preferred embodiments, if $p<\alpha_1$, a "detected" call can be made (i.e., the expression of

the target gene is detected in the sample). If $\alpha_1 \leq p < \alpha_2$, a marginally detected call may be made. If $p \geq \alpha_2$, "undetected call" may be made. The proper choice of significance levels and the thresholds can reduce false calls. In some preferred embodiments, $0<\alpha_1<\alpha_2<0.06$. In some particularly preferred embodiments, α_1 is around 0.04 and α_2 is around 0.06.

In some particularly preferred embodiments, the testing statistic is *median((PM$_i$-MM$_i$)/(PM$_i$=MM$_i$))*. In these embodiments, the threshold value is a constant. Typically, the threshold value is around 0.001 to 0.05. Most preferably, the threshold value is around 0.015.

In another aspect of the invention, computer implemented methods are provided for analyzing gene expression experiments where a transcript is detected with multiple probes. The method include steps of providing a plurality of perfect match intensity values (*PM$_i$*) and background intensity values (*B$_i$*) for the transcript, where each of the *PM$_i$* is paired with its corresponding *B$_i$;* calculating a *p* value using one sided Wilcoxon's signed rank test, wherein the *p* value is for a null hypothesis that θ=a threshold value and an alternative hypothesis that the θ> the threshold value, where the θ is a test statistic for intensity difference between the perfect match intensity values and background intensity values; and indicating whether the transcript is present based upon the *p*-value. In preferred embodiments, the testing statistic is *median(PM$_i$-B$_i$)*.

The threshold value can be zero. However, in preferred embodiments, the threshold value is calculated using $\tau_3 = c_3\sqrt{median(PM_i)}$ where the c_1 is a constant. Alternatively, the threshold value is calculated using: $\tau_3 = c_3\sqrt{mean(PM_i)}$ where the c_3 is a constant.

The presence, marginal present or absence (detected, marginally detected or undetected) of a transcript may be called based upon the *p*–value and significance levels.

Significance levels, α_1 and α_2 may be set such that: $0<\alpha_1<\alpha_2<0.5$. Note that for the one-sided test, if null hypothesis is true, the most likely observed *p*-value is 0.5, which is equivalent to 1 for the two-sided test. Let *p* be the *p*-value of one-sided signed rank test. In preferred embodiments, if $p<\alpha_1$, a "detected" call can be made (i.e., the expression of the target gene is detected in the sample). If $\alpha_1 \leq p <\alpha_2$, a marginally detected call may be made. If $p\geq\alpha_2$, "undetected call" may be made. The proper choice of significance levels and the thresholds can reduce false calls. In some preferred embodiments, $0<\alpha_1<\alpha_2<0.06$. In some particularly preferred embodiments, α_1 is around 0.04 and α_2 is around 0.06.

In another aspect, computer software products are provided. The computer software products include computer program code for inputting a plurality of perfect match intensity values (PM_i) and mismatch intensity values (MM_i) for a transcript, wherein each of the PM_i is paired with one of the MM_i; computer program code for calculating a *p* value using one-sided Wilcoxon's signed rank test, wherein the *p* value is for a null hypothesis that θ=a threshold value and an alternative hypothesis that the θ> the threshold value, wherein the θ is a test statistic for intensity difference between the perfect match intensity values and mismatch intensity values; computer program code for indicating whether the transcript is present based upon the *p* value; and a computer readable media for storing the computer program codes. In some preferred embodiments of the computer software products, the testing statistic is $median(PM_i-MM_i)$. The threshold value may be zero in some embodiments. In preferred embodiments, however,

the threshold value is calculated using $\tau_1 = c_1\sqrt{median(PM_i)}$ where the c_1 is a constant or using $\tau_1 = c_1\sqrt{mean(PM_i)}$ where the c_1 is a constant.

In some particularly preferred embodiments of the computer software products of the invention, the testing statistic is $median((PM_i-MM_i)/(PM_i-MM_i))$ and threshold value is a constant. The computer program product may contain code for accepting user's selection or input of the threshold value. A default value may be used as well. Typically, the threshold value is around 0.001 to 0.05. In a particularly preferred embodiment, the threshold value is around 0.015.

The presence, marginal present or absence (detected, marginally detected or undetected) of a transcript may be called based upon the p –value and significance levels.

Significance levels, α_1 and α_2 may be set such that: $0<\alpha_1<\alpha_2<0.5$. In preferred embodiments, if $p<\alpha_1$, a "detected" call can be made (i.e., the expression of the target gene is detected in the sample). If $\alpha_1 \leq p <\alpha_2$, a marginally detected call may be made. If $p\geq\alpha_2$, "undetected call" may be made. The proper choice of significance levels and the thresholds can reduce false calls. In some preferred embodiments, $0<\alpha_1<\alpha_2<0.06$. In some particularly preferred embodiments, α_1 is around 0.04 and α_2 is around 0.06.

The computer software product may include computer program code for indicating that the transcript is present, absent, or marginally absent. The computer program code, when executed, may indicate the result by causing the display of the result on a display device such as a screen. Alternatively, the result may be outputted into a file. In addition, the result may be temporary stored in a computer memory device so that other computer program module may access this result. In some preferred embodiments, the

computer software products may include code to accept user's selection of various significance levels.

In addition, the present invention includes computer software products for analyzing the presence of a transcript without using mismatch intensities. The computer software product includes computer program code for providing a plurality of perfect match intensity values (PM_i) and background intensity values (B_i) for a transcript, wherein each of the PM_i is paired with one of the B_i; computer program code for calculating a p-value using one-sided Wilcoxon's signed rank test, wherein said p-value is for a null hypothesis that θ=a threshold value and an alternative hypothesis that the θ> the threshold value, where the θ is a test statistic for intensity difference between the perfect match intensity values and background intensity values; and computer program code for indicating whether the transcript is present based upon the p-value; and a computer readable media for storing the codes. The testing statistic may be $median(PM_i\text{-}B_i)$. The threshold value can be zero.

In preferred embodiments, the threshold value is calculated using:

$\tau_3 = c_3\sqrt{median(PM_i)}$ where the c_3 is a constant and alternatively, the threshold value is calculated using: $\tau_3 = c_3\sqrt{mean(PM_i)}$ where the c_3 is a constant.

The computer software product may include computer program code for indicating that the transcript is present, absent or marginally absent . The computer program code, when executed, may indicate the result by causing the display of the result on a display device such as a screen. Alternatively, the result may be outputted into a file. In addition, the result may be temporary stored in a computer memory device so that other

computer program module may access this result. In some preferred embodiments, the computer software products may include code to accept user's selection of various significance levels.

In addition, systems for determining whether a transcript is present in a biological sample are also provided. The systems include a processor; and a memory being coupled to the processor, the memory storing a plurality of machine instructions that cause the processor to perform a plurality of logical steps when implemented by the processor; the logical steps include the method steps of the invention.

VII. Grounds of Rejections to be Reviewed on Appeal

A. Claims 1-2, 6-9, 11-12, 14-15, 26-27, 31-34, 36-40, 44-47, 49-53, 56-69, 61-65, 69-72, 74-78, 82-85, 87-91, and 93-103 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

B. Claims 39-47, 49-51, 52-59, 64-72, and 74-76 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

C. Claims 1, 39, and 77 have been rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Lockhart et al. (1996) in view of either Hogg et al. or Hollander et al.

VIII. Argument

A. The claims meet the Enablement Requirement of 35 U.S.C. 112, first paragraph, that the specification enable any person skilled in the art to make and use the invention.

In this application, claims 1-2, 6-9, 11-12, 14-15, 26-27, 31-34, 36-40, 44-47, 49-53, 56-72, 74-78, 82-85, 87-91, and 93-103 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement.

Section 112 of Title 35 of the United States Code, first paragraph, states that for an intention to be patentable, the specification must enable any person skilled in the art to make and use the invention:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same....

"Paragraph 1 permits resort to material outside of the specification in order to satisfy the enablement portion of [Section 112]." Atmel Corp. v. Information Storage Devices, Inc., 198 F.3d 1374, 1382, 53 U.S.P.Q.2d 1225 (Fed.Cir. 1999). In Atmel Corp., the Federal Circuit noted "[t]he specification would be of enormous and unnecessary length if one had to literally reinvent and describe the wheel." Id. at 1382. Indeed, the specification need only be enabling to persons skilled in the art. Moreover, "[w]hen an invention, in its different aspects, involves distinct arts, that specification is adequate which enables the adepts of each art, those who have the best chance of being enabled, to

carry out the aspect proper to their specialty." In re Naquin, 398 F.2d 863, 866, 158 U.S.P.Q. 317 (C.C.P.A. 1988).

"[E]ven though the statute does not use the term 'undue experimentation,' it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation." Manual of Patent Examining Procedure, § 2164.01, (8th ed. Rev. 2, May 2004). In In re Wands, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed.Cir. 1988), the Federal Circuit identified several factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

> They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. at 737.

However, in that shaping case, it is properly noted that to such person(s) skilled in the art, "experimentation needed to practice the invention must not be undue experimentation" Id. at 736-737,

> [t]hat is not to say that the specification itself must necessarily describe how to make and use every possible variant of the claimed invention, for the artisan's knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments,

depending upon the predictability of the art. AK Steel Corp. v. Sollac, 344 F.3d 1234, 1244, 68 U.S.P.Q.2d 1280 (Fed.Cir. 2003).

Albeit "the enabling disclosure of the specification [must] be commensurate in scope with the claim under consideration", In re Hyatt, 708 F.2d 712, 714, 218 U.S.P.Q. 195 (Fed.Cir. 1983), "[e]ven when the specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using 'words or expressions of manifest exclusion or restriction.'" Liebel-Flarsheim Co. v. Medrad, Inc., 358 F.3d 898, 906, 69 U.S.P.Q.2d 1801 (Fed.Cir. 2004) citing Teleflex, Inc. v. Ficosa N. Am. Corp., 299 F.3d 1313, 1325, 63 U.S.P.Q.2d 1374 (Fed.Cir. 2002). The Federal Circuit has stated that "[t]he enablement requirement is met if the description enables any mode of making and using the claimed invention." Engel Indus., Inc. v. Lockformer Co., 946 F.2d 1528, 1533, 20 U.S.P.Q.2d 1300 (Fed.Cir. 1991).

Claims 1, 26, 39, 64, 77, and 91-103

The Examiner rejected claims 1, 26, 39, 64, 77, and 91-103 on the basis that the specification allegedly does not provide guidance on selecting or developing other test statistics for use in the claimed method nor the associated threshold values. The rejected claims recite calculating a *p*-value using One-Sided Wilcoxon's signed rank test and determining whether a transcript is present in a biological sample based upon the *p*-value, the *p*-value being calculated based upon a test statistic for intensity difference between the perfect match intensity values and mismatch intensity values.

In AK Steel Corp., the Federal Circuit held that the specification needn't describe "how to make and use every possible variant of the claimed invention." AK Steel Corp. at 1244. Notwithstanding the holding of the Federal Circuit in AK Steel Corp, the specification clearly discloses several particular test statistics. Deriving suitable test statistics and meaningful threshold values for One-Sided Wilcoxon's signed rank test is explained in numerous statistical methods textbooks, 3 of which were disclosed by the applicants in their IDS and 2 of which were ironically acknowledged by the Examiner, in her 11/4/02 Office Action, as disclosing the "known nonparametric statistical analysis." Hogg, Probability and Statistical Inference, Ch.10, 5th Ed., Prentice Hall, Inc., 1997; Hollander, Nonparametric Statistical Methods, Ch.3, 2nd Ed., John Wiley & Sons, Inc., 1999; Wilcoxon, "Individual Comparisons by Ranking Methods", Biometrics, Vol. 1, 1945, pps. 80-83; Hogg, Introduction to Mathematical Statistics, Ch.11, 5th Ed., Prentice Hall, Inc., 1995; Cox, Theoretical Statistics, Ch.6, Chapman & Hall/CRC, 1974; Box, Statistics for Experimenters An Introduction to Design, Data Analysis, and Model Building, Ch.3, John Wiley & Sons, Inc., 1978; Balding, Handbook for Statistical Genetics, Vol.1, 2nd Ed., John Wiley & Sons, Ltd., 2003; Armitage, Encyclopedia of Biostatistics, Vol.6, John Wiley & Sons, Ltd., 1998.

The Examiner alleges that the claims should be rejected because "there is no evidence of record that test statistics for intensity differences between perfect match and mismatch probes .... were routinely developed and validated." Applicants respectfully submit that the specification provides a guidance (i.e., the test statistics is about intensity difference) and several specific examples. Page 4 of the original specification, disclosing that the test statistic may be the median of the difference between the perfect match and mismatch

intensity values, and the threshold value may be zero or may be set to be proportional to the square root of either the sample median or mean of perfect match intensity. Page 5 of the specification discloses yet another test statistic and corresponding threshold value. Page 6 discloses that the test statistic may be the median of the difference between the perfect match and background intensity values, and the threshold value may be zero or may be set to be proportional to the square root of either the sample median or mean of perfect match intensity. Additionally, the specification discloses other test statistics such as the discrimination score, also referred to as Ryder's discrimination score (e.g., page 24).

Note also that the present invention is not limited to any particular test statistic or threshold value, but rather a method that uses a suitable test statistic and meaningful threshold value for One-Sided Wilcoxon's signed rank test, with the *suitable test statistic being for intensity difference between the perfect match and mismatch intensity values* as recited in the rejected claims.

In summary, the law does not require the Applicants to disclose every possible variant of the claimed invention. Nevertheless, the specification recites numerous ways of calculating a suitable test statistic for One-Sided Wilcoxon's signed rank test, a routine statistic that is well within the skill of an ordinary artisan in the relevant art to derive, in light of the disclosed direction and examples, without undue experimentation according to the factors set forth in In re Wands, or by any other conceivable standard.

Claims 1-2, 6-9, 11-12, 14-15, 26-27, 31-34, 36-40, 44-47, 49-53, 56-69, 61-65, 69-72, 74-78, 82-85, 87-91, and 93-103

The Examiner rejected claims 1-2, 6-9, 11-12, 14-15, 26-27, 31-34, 36-40, 44-47, 49-53, 56-69, 61-65, 69-72, 74-78, 82-85, 87-91, and 93-103 on the basis that the claims allegedly require a threshold value for the p value without reciting how it is determined. Again, "[t]he enablement requirement is met if the description enables any mode of making and using the claimed invention." Engel Indus., Inc. at 1533. The specification is clear that, among the numerous calculations that may be used to select the threshold value, the threshold value may be zero or may be set to be proportional to the square root of either the sample median or mean of perfect match intensity (e.g., page 29 of the original specification). In addition, the specification provides ample guidance on selecting a specific threshold value (e.g., page 31).

In any case, it made explicitly clear that the threshold value is set according to user preference (e.g., page 31 of the original specification). It is well known in the art and well taught, in among others, the aforementioned statistical methods textbooks, that *p*-value thresholds are selected depending upon, for example, whether a user wants to employ a more stringent or less stringent test. *P*-value is the probability that observed differences (here, between the perfect match and mismatch intensity values) are due to random sampling. It is a routine practice, in many fields of science, including chemical science, for a user to determine and report at what *p*-value the user would accept that the observed differences are not due to random sampling.

In summary, the applicants met their burden of enablement when they set forth a single mode of making and using the claimed invention. Applicants have gone further by setting forth ample guidance pertaining to and additional examples of selecting threshold

values. It is well within the skill of an ordinary artisan in the relevant art to derive, without undue experimentation, in light of the disclosure, meaningful threshold values.

Applicants wish to point out that the initial burden on the examiner under the Enablement Requirement when doubt arises about enablement: "In such a case, the examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation." Manual of Patent Examining Procedure, § 2164.04 (8th ed. Rev. 2, May 2004).

> When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. If the PTO meets this burden, the burden then shifts to the applicant to provide suitable proofs indicating that the specification is indeed enabling. In re Wright, 999 F.2d 1557, 1561-1562, 27 U.S.P.Q.2d 1510 (Fed.Cir. 1993).

Applicants respectfully submit that the Examiner has made no such reasonable showing and that each of the claims on appeal herein are enabling to those of ordinary skill in the art as of the time the invention was made.

B. The claims meet the requirement of 35 U.S.C. 112, second paragraph, that the claims particularly point out and distinctly claim the subject matter which the applicant regards as his invention.

Claims 39-47, 49-51, 52-59, 64-72, and 74-76

In this application, claims 39-47, 49-51, 52-59, 64-72, and 74-76 were rejected under 35 U.S.C. 112, second paragraph, for allegedly being indefinite.

Section 112 of Title 35 of the United States Code, second paragraph, states that for an intention to be patentable, the claims must particularly point out and distinctly claim the subject matter which the applicant regards as his invention:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The Examiner alleged that claims 39 and 64 remain confusing as to whether the software product is an integrated product. Applicants maintain their argument that the claim clearly recites "a computer software product", and that the plain meaning of the claim language is that it is a single software product.

Applicants respectfully submit that each of the claims on appeal herein do in fact particularly point out and distinctly claim the subject matter which the applicant regards as his invention.

C. The claims meet the requirement of 35 U.S.C. 103(a), that that the subject matter as a whole must not have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Claims 1, 39, and 77

Claims 1, 39, and 77 were rejected under 35 U.S.C. 103 (a) as allegedly being unpatentable over Lockhart et al. (1996) in view of either Hogg et al. or Hollander et al.

Section 103(a) of Title 35 of the United States Code, states that for an intention to be patentable, the subject matter as a whole must not have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Lockhart, et al. discloses quantitative analysis of the signal intensity of PM and MM pairs from an array hybridization experiment. Hogg et al. and Hollander et al. are two statistical methods textbooks that, among other things, disclose Wilcoxon's signed rank test and its use for interpreting nonparametric data. Applicants respectfully submit that the Examiner has failed to establish a prima facie case because there was no teaching, suggestion or motivation in the cited references that nonparametric tests are suitable for analyzing probe level data.

The current application is directed towards analyzing probe level data. The Examiner alleges that one of ordinary skill in the art would have been aware that hybridization data from nucleic acid arrays was nonparametric data, and as such, it would have been obvious to use known nonparametric statistical analysis to analyze the results of multiple probe experiments for perfect match and mismatch probes. Applicants respectfully submit that the Office Action fails to point out the basis of the allegation that one of ordinary skill in the art, at the time of the invention, would have known that hybridization data is nonparametric. The Office Action also fails to indicate how the nonparametric nature of hybridization data would lead to the employment of Wilcoxon's tests for analyzing intensity differences.

Applicants respectfully submit that each of the claims on appeal herein were not obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Because no rejection under 35 U.S.C. 103(a) was made by the Examiner as to any other claim, if it is found that the 3 claims on appeal herein are allowable, it follows that all claims which depend from those 3 claims, 2-9, 11-21, 23-25, 40-47, 49-59, 61-63, 78-85, 87-97, and 99-101 are also allowable as not obvious at the time the invention was made to a person having ordinary skill in the art.

IX. Claims Appendix

A listing of the claims which are the subject of this appeal are set forth below. The claims herein include all amendments.

X. Conclusion

Applicants respectfully submit that each of the claims on appeal herein are enabling to those of ordinary skill in the art as of the time the invention was made, particularly point out and distinctly claim the subject matter which the applicant regards as his invention, and were not obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Accordingly, the examiner's final rejection of the claims should be reversed and each of the claims passed to allowance.

Respectfully submitted,

By _____ 6/24/05
Wei Zhou Reg. 44,419

Attachment – Claims Appendix

Customer No.: 22886
Legal Department
Affymetrix, Inc.
3380 Central Expressway
Santa Clara, CA 95051
Tel: 408/731-5000
Fax: 408/731-5392

CLAIMS APPENDIX

Listing of claims:

1. (Original) A method for determining whether a transcript is present in a biological sample comprising:

providing a plurality of perfect match intensity values (PM_i) and mismatch intensity values (MM_i) for the transcript, wherein each of the PM_i is paired with one of the MM_i;

calculating a p-value using one-sided Wilcoxon's signed rank test, wherein the p-value is for a null hypothesis that θ=a threshold value and an alternative hypothesis that said θ> said threshold value, wherein said θ is a test statistic for intensity difference between said perfect match intensity values and mismatch intensity values; and

indicating whether said transcript is present based upon said p-value.

2. (Original) The method of Claim 1 wherein said testing statistic is $median(PM_i\text{-}MM_i)$.

3. (Original) The method of Claim 2 wherein said threshold value is zero.

4. (Original) The method of Claim 2 wherein said threshold value is calculated using: $\tau_1 = c_1\sqrt{median(PM_i)}$ wherein said c_1 is a constant.

5. (Original) The method of Claim 2 wherein threshold value is calculated using: $\tau_1 = c_1\sqrt{mean(PM_i)}$ wherein said c_1 is a constant.

6. (Original) The method of Claim 2 wherein said step of indicating comprises indicating said transcript is present if said p is smaller than a first significance level (α_1).

7. (Original) The method of Claim 6 wherein said significance level is 0.01-0.08.

8. (Original) The method of Claim 7 wherein said first significance level is 0.04.

9. (Original) The method of Claim 7 wherein said step of indicating further comprises indicating said transcript is absent if said p is greater than or equal to a second significance level (α_2).

10. (Canceled)

11. (Previously presented) The method of Claim 9 wherein said second significance level is 0.06.

12. (Original) The method of Claim 11 wherein said first significance level (α_1) is smaller than said (α_2) and said step of indicating further comprises indicating said transcript is marginally detected if $\alpha_1 \leq p < \alpha_2$.

13. (Original) The method of Claim 12 where first significance level is 0.04 and second significance level is 0.06.

14. (Previously presented) The method of Claim 1 wherein said testing statistic is $median((PM_i\text{-}MM_i)/(PM_i + MM_i))$.

15. (Original) The method of Claim 14 wherein said threshold value is a constant.

16. (Original) The method of Claim 15 wherein said threshold value is around 0.001 to 0.05.

17. (Original) The method of Claim 16 wherein said threshold value is around 0.015.

18. (Original) The method of Claim 17 wherein said step of indicating comprises indicating said transcript is present if said p is smaller than a first significance level (α_1).

19. (Original) The method of Claim 18 wherein said significance level is 0.01-0.08.

20. (Original) The method of Claim 19 wherein said first significance level is 0.04.

21. (Original) The method of Claim 20 wherein said step of indicating further comprises indicating said transcript is absent if said p is greater than a second significance level (α_2).

22. (Canceled)

23. (Previously presented) The method of Claim 21 wherein said second significance level is 0.06.

24. (Previously presented) The method of Claim 21 wherein said first significance level (α_1) is smaller than said (α_2) and said step of indicating further comprises indicating said transcript is marginally detected if $\alpha_1 \leq p < \alpha_2$.

25. (Original) The method of Claim 24 where first significance level is 0.04 and second significance level is 0.06.

26. (Original) A method for determining whether a transcript is present in a biological sample comprising:

providing a plurality of perfect match intensity values (PM_i) and background intensity values (B_i) for said transcript, wherein each of said PM_i is paired with one of said B_i;

calculating a p value using one sided Wilcoxon's signed rank test, wherein said p value is for a null hypothesis that θ=a threshold value and an alternative hypothesis that said θ> said threshold value, wherein said θ is a test statistic for intensity difference between said perfect match intensity values and background intensity values; and

indicating whether said transcript is present based upon said *p* value.

27. (Original) The method of Claim 26 wherein said testing statistic is $median(PM_i\text{-}B_i)$.

28. (Original) The method of Claim 27 wherein said threshold value is zero.

29. (Previously presented) The method of Claim 27 wherein said threshold value is calculated using: $\tau_3 = c_3\sqrt{median(PM_i)}$ wherein said c_3 is a constant.

30. (Original) The method of Claim 27 wherein threshold value is calculated using: $\tau_3 = c_3\sqrt{mean(PM_i)}$ wherein said c_3 is a constant.

31. (Original) The method of Claim 27 wherein said step of indicating comprises indicating said transcript is present if said *p* is smaller than a first significance level (α_1).

32. (Original) The method of Claim 31 wherein said significance level is 0.01-0.08.

33. (Original) The method of Claim 32 wherein said first significance level is 0.04.

34. (Original) The method of Claim 31 wherein said step of indicating further comprises indicating said transcript is absent if said *p* is greater than a second significance level (α_2).

35. (Canceled)

36. (Previously presented) The method of Claim 34 wherein said second significance level is 0.06.

37. (Previously presented) The method of Claim 34 wherein said first significance level (α_1) is smaller than said (α_2) and said step of indicating further comprises indicating said transcript is marginally detected if $\alpha_1 \leq p < \alpha_2$.

38. (Original) The method of Claim 37 where first significance level is 0.04 and second significance level is 0.06.

39. (Previously presented) A computer software product comprising:

computer program code for inputting a plurality of perfect match intensity values (PM_i) and mismatch intensity values (MM_i) for a transcript, wherein each of said PM_i is paired with one of said MM_i;

computer program code for calculating a p value using one sided Wilcoxon's signed rank test, wherein said p value is for a null hypothesis that θ=a threshold value and an alternative hypothesis that said θ> said threshold value, wherein said θ is a test statistic for intensity difference between said perfect match intensity values and mismatch intensity values;

computer program code for indicating whether said transcript is present based upon said p value; and

a computer readable medium that stores said computer program codes.

40. (Original) The computer software product of Claim 39 wherein said testing statistic is $median(PM_i\text{-}MM_i)$.

41. (Original) The computer software product of Claim 40 wherein said threshold value is zero.

42. (Original) The computer software product of Claim 40 wherein said threshold value is calculated using: $\tau_1 = c_1\sqrt{median(PM_i)}$ wherein said c_1 is a constant.

43. (Previously presented) The computer software product of Claim 40 wherein threshold value is calculated using: $\tau_1 = c_1\sqrt{mean(PM_i)}$ wherein said c_1 is a constant.

44. (Original) The computer software product of Claim 40 wherein said computer program code of indicating comprises computer program code for indicating that said transcript is present if said p is smaller than a first significance level (α_1).

45. (Original) The computer software product of Claim 44 wherein said significance level is 0.01-0.08.

46. (Original) The computer software product of Claim 45 wherein said first significance level is 0.04.

47. (Original) The computer software product of Claim 46 wherein said computer code for indicating further comprises computer program code for indicating that said transcript is absent if said p is greater than or equal to a second significance level (α_2).

48. (Canceled)

49. (Previously presented) The computer software product of Claim 47 wherein said second significance level is 0.06.

50. (Original) The computer software product of Claim 49 wherein said first significance level (α_1) is smaller than said (α_2) and said computer program code of indicating further comprises computer program code for indicating that said transcript is marginally detected if $\alpha_1 \leq p < \alpha_2$.

51. (Original) The computer software product of Claim 50 where first significance level is 0.04 and second significance level is 0.06.

52. (Previously presented) The computer software product of Claim 40 wherein said testing statistic is $median((PM_i-MM_i)/(PM_i+MM_i))$.

53. (Original) The computer software product of Claim 52 wherein said threshold value is a constant.

54. (Original) The computer software product of Claim 53 wherein said threshold value is around 0.001 to 0.05.

55. (Original) The computer software product of Claim 54 wherein said threshold value is around 0.015.

56. (Original) The computer software product of Claim 53 wherein said computer program code for indicating comprises computer program code for indicating that said transcript is present if said p is smaller than a first significance level (α_1).

57. (Original) The computer software product of Claim 56 wherein said significance level is 0.01-0.08.

58. (Original) The computer software product of Claim 57 wherein said first significance level is 0.04.

59. (Original) The computer software product of Claim 57 wherein said computer program code for indicating further comprises computer program code for indicating said transcript is absent if said p is greater than or equal to a second significance level (α_2).

60. (Canceled)

61. (Previously presented) The computer software product of Claim 59 wherein said second significance level is 0.06.

62. (Previously presented) The computer software product of Claim 59 wherein said first significance level (α_1) is smaller than said (α_2) and said computer program code for indicating further comprises computer code for indicating that said transcript is marginally detected if $\alpha_1 \leq p < \alpha_2$.

63. (Original) The computer software product of Claim 62 where first significance level is 0.04 and second significance level is 0.06.

64. (Previously amended) A computer software product comprising:

computer program code for providing a plurality of perfect match intensity values (PM_i) and background intensity values (B_i) for a transcript, wherein each of said PM_i is paired with one of said B_i;

computer program code for calculating a p value using one sided Wilcoxon's signed rank test, wherein said p-value is for a null hypothesis that θ=a threshold value and an alternative hypothesis that said θ> said threshold value, wherein said θ is a test statistic for intensity difference between said perfect match intensity values and background intensity values; and

computer program code for indicating whether said transcript is present based upon said p-value; and

a computer readable medium that stores said codes.

65. (Original) The computer software product of Claim 64 wherein said testing statistic is $median(PM_i\text{-}B_i)$.

66. (Original) The computer software product of Claim 65 wherein said threshold value is zero.

67. (Previously presented) The computer software product of Claim 66 wherein said threshold value is calculated using: $\tau_3 = c_3\sqrt{median(PM_i)}$ wherein said c_3 is a constant.

68. (Original) The computer software product of Claim 66 wherein threshold value is calculated using: $\tau_3 = c_3\sqrt{mean(PM_i)}$ wherein said c_3 is a constant.

69. (Original) The computer software product of Claim 66 wherein said step of indicating comprises indicating said transcript is present if said p is smaller than a first significance level (α_1).

70. (Original) The computer software product of Claim 69 wherein said significance level is 0.01-0.08.

71. (Original) The computer software product of Claim 70 wherein said first significance level is 0.04.

72. (Original) The computer software product of Claim 71 wherein said computer software code of indicating further comprises computer software code for indicating that said transcript is absent if said p is greater than or equal to a second significance level (α_2).

73. (Canceled)

74. (Previously presented) The computer software product of Claim 72 wherein said second significance level is 0.06.

75. (Previously presented) The computer software product of Claim 72 wherein said first significance level (α_1) is smaller than said (α_2) and said code for indicating further comprises code for indicating that said transcript is marginally detected if $\alpha_1 \leq p < \alpha_2$.

76. (Original) The computer software product of Claim 75 where first significance level is 0.04 and second significance level is 0.06.

77. (Previously presented) A system for determining whether a transcript is present in a biological sample comprising:

a processor; and

a memory being coupled to the processor, the memory storing a plurality of machine instructions that cause the processor to perform a plurality of logical steps when implemented by the processor, said logical steps comprising:

providing a plurality of perfect match intensity values (PM_i) and mismatch intensity values (MM_i) for the transcript, wherein each of the PM_i is paired with one of the MM_i;

calculating a p-value using one-sided Wilcoxon's signed rank test, wherein the p-value is for a null hypothesis that θ=a threshold value and an alternative hypothesis that said θ> said threshold value, wherein said θ is a test statistic for intensity difference between said perfect match intensity values and mismatch intensity values; and

indicating whether said transcript is present based upon said p-value.

78. (Original) The system of Claim 77 wherein said testing statistic is $median(PM_i\text{-}MM_i)$

79. (Original) The system of Claim 78 wherein said threshold value is zero.

80. (Original) The system of Claim 78 wherein said threshold value is calculated using: $\tau_1 = c_1\sqrt{median(PM_i)}$ wherein said c_1 is a constant.

81. (Original) The system of Claim 78 wherein threshold value is calculated using: $\tau_1 = c_1\sqrt{mean(PM_i)}$ wherein said c_1 is a constant.

82. (Original) The system of Claim 78 wherein said step of indicating comprises indicating said transcript is present if said p is smaller than a first significance level (α_1).

83. (Original) The system of Claim 82 wherein said significance level is 0.01-0.08.

84. (Original) The system of Claim 83 wherein said first significance level is 0.04.

85. (Original) The system of Claim 83 wherein said step of indicating further comprises indicating said transcript is absent if said p is greater than or equal to a second significance level (α_2).

86. (Canceled)

87. (Previously presented) The system of Claim 85 wherein said second significance level is 0.06.

88. (Original) The system of Claim 87 wherein said first significance level (α_1) is smaller than said (α_2) and said step of indicating further comprises indicating said transcript is marginally detected if $\alpha_1 \leq p < \alpha_2$.

89. (Original) The system of Claim 88 where first significance level is 0.04 and second significance level is 0.06.

90. (Previously presented) The computer software product of Claim 76 wherein said testing statistic is $median((PM_i-MM_i)/(PM_i+MM_i))$.

91. (Original) The system of Claim 77 wherein said threshold value is a constant.

92. (Original) The system of Claim 91 wherein said threshold value is around 0.001 to 0.05.

93. (Original) The system of Claim 92 wherein said threshold value is around 0.015.

94. (Original) The system of Claim 91 wherein said step of indicating comprises indicating said transcript is present if said p is smaller than a first significance level (α_1).

95. (Original) The system of Claim 94 wherein said significance level is 0.01-0.08.

96. (Original) The system of Claim 95 wherein said first significance level is 0.04.

97. (Original) The system of Claim 96 wherein said step of indicating further comprises indicating said transcript is absent if said p is greater than a second significance level (α_2).

98. (Canceled)

99. (Previously presented) The system of Claim 97 wherein said second significance level is 0.06.

100. (Previously presented) The system of Claim 97 wherein said first significance level (α_1) is smaller than said (α_2) and said step of indicating further comprises indicating said transcript is marginally detected if $\alpha_1 \leq p < \alpha_2$.

101. (Original) The system of Claim 100 where first significance level is 0.04 and second significance level is 0.06.

102. (Previously presented) A system for determining whether a transcript is present in a biological sample comprising:

a processor; and

a memory being coupled to the processor, the memory storing a plurality of machine instructions that cause the processor to perform a plurality of

logical steps when implemented by the processor; said logical steps comprising:

providing a plurality of perfect match intensity values (PM_i) and background intensity values (B_i) for said transcript, wherein each of said PM_i is paired with one of said B_i;

calculating a p value using one sided Wilcoxon's signed rank test, wherein said p value is for a null hypothesis that θ=a threshold value and an alternative hypothesis that said θ> said threshold value, wherein said θ is a test statistic for intensity difference between said perfect match intensity values and background intensity values; and

indicating whether said transcript is present based upon said p value.

103. (Previously presented) A method for determining whether a transcript is present in a biological sample comprising:

providing a plurality of perfect match intensity values (PM_i) and mismatch intensity values (MM_i) for more than 5000 transcripts, wherein the PM_i for each of said 5000 transcripts is paired with one of the MM_i;

calculating a p-value using one-sided Wilcoxon's signed rank test, wherein the p-value is for a null hypothesis that θ=a threshold value and an alternative hypothesis that said θ> said threshold value, wherein said θ is a test statistic for intensity difference between said perfect match intensity values and mismatch intensity values; and

indicating whether said transcript is present based upon said p-value.